FOOD AND DRUG ADMINISTRATION

SIXTY-EIGHTH MEETING

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

- - -

AFTERNOON SESSION

8:33 a.m.

Monday, September 10, 2001

Versailles Ballroom
Holiday Inn - Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

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ATTENDEES (Continued)

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BARRY L. WENIG, M.D., M.P.H.

ALSO PRESENT:

RICHARD W. CURRY
EDWARD F. McCARTAN
KIM THIBOLDEAUX

C O N T E N T S

AFTERNOON SESSION

NDA 21-236
IntraDose (cisplatin/epinephrine) Injectable Gel
Matrix Pharmaceutical, Inc.

C O N T E N T S (Continued)

AFTERNOON SESSION

(1:35 p.m.)

DR. NERENSTONE: Good afternoon. I think we're going to get started in the afternoon session. From our agenda it's going to be discussion of the cisplatin/epinephrine injectable gel.

We'd like to start by going around the table, if everyone could introduce themselves and tell us where they're from. Dr. Glisson, if you'd like to start.

DR. GLISSON: Bonnie Glisson, M.D. Anderson Cancer Center in head and neck medical oncology.

DR. KELSEN: David Kelsen, Sloan-Kettering.

DR. ALBAN: Kathy Alban, medical oncology, Loyola University, Chicago.

MR. GRUETT: Glenn Gruett, patient representative from Appleton, Wisconsin.

DR. LIPPMANN: Scott Lippmann, M.D. Anderson Cancer Center.

DR. CARPENTER: John Carpenter from the University of Alabama at Birmingham.

DR. PRZEPIORKA: Donna Przepiorka, Baylor College of Medicine, Houston.

DR. NERENSTONE: Stacy Nerenstone, medical oncologist, Hartford, Connecticut.

DR. SLEDGE: George Sledge, medical oncologist,

Indiana University.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner, Phoenix Indian Medical Center, and I'm the consumer rep.

DR. RUBENSTEIN: Larry Rubenstein, biostatistician, National Cancer Institute.

DR. REDMAN: Bruce Redman, University of Michigan Cancer Center.

DR. COUCH: Marion Couch, head and neck surgery, Johns Hopkins Hospital.

DR. BLAYNEY: Doug Blayney, medical oncologist, Wilshire Oncology Medical Group, Pasadena, California.

DR. SRIDHARA: Raje Sridhara, FDA.

DR. FRYKMAN: Gregory Frykman, medical officer, FDA.

DR. WILLIAMS: Grant Williams, medical team leader.

DR. PAZDUR: Richard Pazdur, division director, FDA.

MR. TEMPLE: Bob Temple, office director, FDA.

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and the information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions. Stephen George, Ph.D., and Sarah Taylor, M.D., are recused from participating in the discussions and vote concerning IntraDose.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. NERENSTONE: We're going to turn to our open public hearing. Mr. McCartan.

MR. McCARTAN: Good afternoon. Can I be heard in the back? I assume so. My name is Ed McCartan. First I want to thank the FDA for giving me the opportunity to appear before this distinguished panel.

I'm here as a 15-year survivor of head and neck cancer and to advocate for non-invasive or less invasive treatment of head and neck and oral cancer in order to minimize the damaging effects of the current treatments and also to provide palliative care for those in extreme circumstances.

Matrix Pharmaceutical has made a start in this direction with IntraDose, which as I understand it, is a gel which can be injected directly into the cancer.

Matrix, incidentally, has provided my transportation expenses to and from New York. But I'm not representing any particular cancer-related organization. I am here as an individual to speak for survivors and for those facing treatment who will become survivors.

My credentials come from a long-time association with support groups in New York City mostly. I have been associated with the National Coalition for Cancer Survivorship, with Cancer Care. I have been on advisory panels with the Cancer Information Service, and have volunteered for 13 years at the post-treatment resource program at Memorial Sloan-Kettering. So, my outlook and ideas have been formed by that experience and from listening to, talking to, and reading about hundreds of survivors. So, I think I can speak for them.

The current treatment for head and neck cancer

is, of course, radiation, surgery, and chemotherapy in various combinations and degrees. The same treatments, of course, are used for other cancers, but the problem for us as survivors is the damage that is done to the head and neck, organs, nerves, and bones as a result of the treatment. I think most of us have gone through dry mouths, a variety of pain, loss of taste and smell, loss of hair, nausea, depression, and difficulty in chewing and swallowing. These results can last for months and for even years, and beyond that there are permanent problems, such as loss of speech when associated with cancer of the larynx. Damage to hearing and sight and to the teeth and to the jaw and sometimes the necessity to take nourishment through a tube in the stomach.

There have been many advances in treatment over the last decade. There is more precise surgery, more focused radiation, and more tolerable chemotherapy, but still the damage occurs. It would be wonderful if the pain and damage could be minimized or avoided by treating with non-invasive items such as drugs and medication. As it stands now, many survivors have told me in sincerity that if they had known what was going to happen to them after the treatment, they would have refused treatment, and I know people who have refused treatment because of what they feared the results would be. This is what we hope to avoid.

You may wonder why I'm speaking for survivors when we've already been through the after-effects. Well, the obvious answer to that is that we all face recurrence, and certainly I wouldn't want to go through the experience again. And knowing what we do, we certainly wouldn't want those undergoing treatment to face the same experience if there is another way. It is that other way that I hope the panel will help to bring about. So, thank you.

Are there any questions?

Thank you.

DR. NERENSTONE: Thank you very much.

Mr. Curry is our next speaker.

MR. CURRY: Thank you for inviting me here. My name is Richard Curry and I want to talk to you about my father and how IntraDose helped to give him three or four good months of life.

I'd like to say first that I have no financial interest in Matrix Pharmaceutical, although Matrix did provide for travel expenses to come to this meeting.

My father's name is Anderson Rudolph Curry. He spent all of his life as a carpenter until he retired. He took a great deal of pleasure in building things. He was a strong man. He worked in the sun. He smoked cigarettes. He liked to play golf. And he enjoyed being with people.

He was a member of the American Legion and the

VFW, with a lifetime membership in both. He was a veteran of World War II. And he liked to have a drink every now and then. He'd often cook for the American Legion, and got involved in many charitable events in his community.

He was 72 years old when he was diagnosed with cancer of the larynx in 1992. He underwent radiation therapy and had a complete response.

Two years later I remember taking him to the hospital after it was determined that the cancer had returned. He had to have his larynx removed and he had a tracheotomy. He was in the hospital for weeks. The surgery devastated him, both mentally and physically.

After surgery, the amount of time he was able to spend with his friends and communicate with them declined dramatically. He didn't like to leave the house, and it was painful for him to play golf. I think he was very self-conscious because he couldn't speak well.

Dad had to return to the hospital every few months for a procedure that would dilate his throat so he could swallow. In 1996 the doctors found recurrent head and neck cancer. They said he couldn't dilate his throat anymore and they put a feeding tube in his stomach.

In September of 1996, they really didn't expect him to live for three or four more months, but he used that feeding tube for more than eight months. He did not want

to have chemotherapy. He didn't want anything to do with chemotherapy because of the side effects, and he was already devastated from the surgery.

In September of 1996, his doctor at the VA hospital told him about a clinical study with IntraDose that was going on at the Tucson VA hospital, and Dad wanted to become a part of this study. The doctor involved in the study in Tucson, Dr. Gerwald, is a medical oncologist. He said it was a double-blind study, where even the doctor would not know if he was getting the drug or the placebo.

Dad was looking forward to possibly feeling better, not for a cure. He was hoping that there would be something he could do to improve the quality of life, or maybe just extend it a little bit. He also wanted to be able to help someone else by what was being learned by his taking part in the study.

The first thing that had to be considered was how he was going to get to Tucson and back. I agreed to drive him to all of his treatments. I looked forward to the time that we were able to spend together, and I wanted to be a part of what he was experiencing and share with him the time that I could. I was glad to see that he had chosen to do something that could help someone else, and to that end, I wanted to help him as much as possible.

He received a total of six treatments with

IntraDose over about two months. With the first treatment, there was some swelling, but I don't recall there being any major reaction to the injection. Of course, it was uncomfortable with somebody sticking a needle in his neck repeatedly, but not debilitating. Later, after the second or third treatment, the pain was worse, so they gave him morphine. He seemed to get some relief from that, and he indicated that he felt pretty uncomfortable the first day or two after the treatment, but he was always ready to go back for the next treatment.

Dad said at one point, it feels uncomfortable but it feels like it's healing. You know what I mean? It doesn't feel good but more of a healing pain.

I never heard him complain about nausea during the treatment with IntraDose, and after the third injection the tumor changed color. It turned black. It developed a big scab, and it eventually healed. It was like the whole tumor had died.

Dr. Gerwald had been concerned that the tumor would block his tracheotomy opening and make it hard for him to breathe, but the treatment seemed to prevent that.

By the time they were into the fifth week, I think he was feeling better. His attitude had changed and he knew that he had been given a little more time. He was going out to play golf, and he started fishing again, and

he was visiting his friends.

Before the treatment with IntraDose, my father's quality of life had gotten worse, and as the cancer had progressed over four years, Dr. Gerwald and his staff were not waiting for him to die. They were waiting for him to respond, and that was a big difference. When he did respond, there was joy for everyone at that point.

If IntraDose had been available when the tumor was discovered, I'm sure he would have used it. It had given him three or four good months of life, and they were good times for me and the people who knew my father. I really hope that this treatment will be available to people like my father. He got better during those treatments. And if it could help someone else, it really should be on the market.

Thank you.

Are there any questions? Thank you.

DR. NERENSTONE: Thank you very much, Mr. Curry.

Our next speaker is Kim Thiboldeaux.

MS. THIBOLDEAUX: Good afternoon. Thank you for the opportunity to be here today. My name is Kim Thiboldeaux and I am the president and CEO of a national nonprofit organization called the Wellness Community.

For the record, the Wellness Community receives

no funding from Matrix Pharmaceutical, and Matrix did not pay for any travel or expenses related to my presence here today.

By way of background, the Wellness Community provides education, support, and hope to people with cancer and their loved ones. We currently have 20 facilities nationwide, four facilities in development in the U.S., and two facilities abroad. Our program includes support groups, educational seminars, nutritional workshops, exercise programs, and mind/body programs. We served an estimated 18,000 people with cancer in the year 2000, and these individuals made over 150,000 visits to our facilities.

At the Wellness Community, we serve people with all cancers at any stage of the disease. We see a wide range of diagnoses, and have had the opportunity to provide direct services to people with head and neck cancer.

While there are currently more than 160,000 people living with head and neck cancer in the U.S., the prognosis for this patient population has not significantly improved over the past 30 years. In addition, as you know, head and neck cancer can be a particularly devastating diagnosis, oftentimes causing facial and other deformities and interfering with basic functions such as breathing, talking, and swallowing. The psychological and emotional

impact of this disease can be quite distressing, leaving little hope for the future.

We are in great need of improved treatment options and disease management tools for people with head and neck cancer. It is critical that new treatments not only fight the cancer, but also allow patients to experience a meaningful quality of life, whether that means continuing to work, traveling, enjoying time with family, or just taking a stroll in the park.

We are also in need of treatment options that are more targeted and can become an alternative to the disfiguring surgery that often accompanies the diagnosis of head and neck cancer. With rapid advances in cancer treatment, we are optimistic that the experimental therapies of today will quickly become the standard of care of tomorrow. We are also optimistic that physicians will engage cancer patients in an open dialogue about goals of treatment, lifestyle concerns, quality of life, side effect management, and other supportive care issues related to a cancer diagnosis.

I would ask today that you carefully consider the plight of patients with head and neck cancer and endeavor to understand the range of both medical and psychosocial issues these patients confront on a daily basis. I would ask today that you seriously consider the

need these patients have for a broader range of treatment options and better tools to manage their disease. And I would ask today that you take a leadership role in encouraging patients to be educated, empowered, and optimistic about the cancer community's commitment to improving the lives of all people with cancer.

Thank you.

DR. NERENSTONE: Thank you very much.

Our next presenter, Mr. Findlay. It's a video.

MR. FINDLAY: My name is Ian Stewart Findlay. I am 59 years old.

I have no financial interest in Matrix Pharmaceutical. Matrix was, however, kind enough to provide resources to videotape my testimony to be given before the FDA.

I am an engineer for Boeing in Huntington Beach, California. I work on the Space Station and on the Delta 4 program.

Today I want to talk to you about my experience with IntraDose. I discovered I had cancer in 1992. I was rock climbing in Yosemite. I didn't seem to have the energy that I normally have. I went to UCLA and the head and neck clinic took six spine needle extracts and told me a week later that I had squamous cell carcinoma in the large lymph nodes in the left neck.

Within a month I had radical neck surgery. They took out 49 lymph nodes. They recommended I follow up the surgery with either radiation or chemotherapy. I decided I didn't like the effects of either of these two treatments, so I said, no, thank you.

I was okay for about two years, and then I started getting some more lumps in the same left neck area. So, I went to Hope Presbyterian Hospital in Newport Beach, California, and I received regular systematic carboplatinum and 5-FU chemotherapy for about two months.

Again, two years -- well, actually it was about two years ago the tumors started coming back in the same left neck area. Just about that same time, I heard that Dr. Dan Castro, a head and neck surgeon at UCLA that was involved with administering a drug in a trial that meant direct injection into tumors. I heard it didn't knock your immunity system the way normal chemical therapy does, and the shrinkage of the tumors, in comparison to regular chemo, is fairly quick. So, I thought, well, I don't have anything to lose. I might as well try this new treatment.

My tumors were fairly good size. They had started restricting my mobility and interfering with all the sports that I was doing, so I had to stopp the sports.

Dr. Castro treated me once a week with the Matrix drug on the left side of the face and the neck. He

said that if we could decrease the size of the tumors with the IntraDose, then it would be easier for him to follow up with surgery and/or radiation.

I kept working during the treatments. I didn't expect the treatments to totally eradicate the cancer, but I did expect it to reduce the size of the tumors, and it did. The tumors were always going down, and this made me pretty happy. This was great. My attitude started to improve.

The treatments caused quite a bit of discomfort for about two days. I would feel a mild stinging and warmness, but that was tolerable. I also experienced a little nausea -- I would say on a scale of 1 to 10 a 3 -- but only a couple of times. I don't ever remember my appetite being affected. I eat like a horse and I didn't lose any weight, unfortunately. My treatment did bother me some. I felt nausea and lightheadedness for about a day, but that was only one time. That time I experienced a stinging sensation at the injection site, but when I took pain pills, they reduced the pain to minor discomfort.

Both the radiation and normal systemic chemotherapy affected me much more than IntraDose in terms of my ability to work and function. I was certainly miserable enough during the radiation and the chemo to need to work part-time, and a nap in the afternoon was

necessary. During the IntraDose injection treatment, I didn't have to do that. The treatment was less disruptive and not as discomforting in terms of weight loss, nausea and fever. Also, the shrinkage of the tumors was dramatically visible, so that was very satisfying. For these reasons I would think it would be a good option for cancer patients.

If I could speak to the FDA directly, I would say that of all the treatment options I've tried, the IntraDose definitely had the most dramatic and quick results, and it didn't knock down my immunity system like the systemic chemotherapy. If I had the opportunity, I probably would not have done the radical surgery. I would have tried the direct injection of IntraDose. I was very pleased when Dr. Castro started the treatments and I began to see these large tumors diminish.

In closing, I would like to urge the FDA to approve this drug in the hope that it can help other head and neck cancer patients.

DR. NERENSTONE: We'll turn now to the sponsor's presentation.

DR. HOWELL: Good afternoon, ladies and gentlemen. It's my pleasure to open the presentation of NDA 21-236, cisplatin/epinephrine gel, for the treatment of squamous cell carcinoma of the head and neck.

My name is Stephen Howell. I'm a professor of medicine and medical oncologist at the University of California, San Diego, where I run the cancer pharmacology program for the UCSD Cancer Center.

I'm here today because of a longstanding interest in regional therapy and because I've been working with a team at Matrix Pharmaceutical for a number of years on the concepts underlying the product that we will hear about today.

The presentation today will consist of a discussion of the current management of recurrent head and neck cancer by Dr. Glenn Mills, who is a medical oncologist and professor of medicine, also head of the aerodigestive malignancy program at Louisiana State University. I will return to discuss the pharmacologic rationale and some of the challenges associated with the assessment of clinical benefit in these patients. Then Dr. Richard Leavitt from Matrix will present the clinical study results, and I will return again to discuss some of the clinical benefit issues. And finally Dr. Glenn Mills will finish up the presentation by discussing the risks and benefits of this product.

We are accompanied today by a number of independent experts who are available to answer questions about the disease. Dr. Everett Vokes, who is head of

hematology/oncology at the University of Chicago, and sub-Chair of the Head and Neck Cancer Committee for RTOG. Dr. Barry Wenig, who is professor of otolaryngology and Chief of the Division of Head and Neck Surgery at Northwestern. Dr. John Mackowiak, Director of Research at the Center for Outcomes Research in Chapel Hill. Dr. John Durant, former Director of both Fox Chase and the University of Alabama Cancer Center, and Chairman of Clinical Cooperative Group, a past chairman and executive at ASCO. And Dr. Robert Woolson, professor and past Chair of Biostatistics at University of Iowa.

We are also accompanied by other staff from Matrix Pharmaceutical, Dr. Laurence Elias, who is the Nedical Director who has handled the safety analysis of this product. Dr. Morgan Stewart, Senior Director of Biostatistics, who has handled the biostatistical analysis of this product. And Dr. Robert Tressler, who has handled the preclinical studies.

I'll now turn the podium to Dr. Mills.

DR. MILLS: Thank you, Dr. Howell. As Dr. Howell told you, I'm Glenn Mills from LSU-Shreveport, where I head up the head and neck program at Shreveport. Also, I'm a PI for SWOG.

What is the scope of the problem we're talking about today? It's estimated in this year, total, there

will be about 50,000 new cases of head and neck cancer that we're going to see, at all sites, today. Of this group of patients, we estimate that there will be about 15,000 deaths from this disease this year. Of those people that die, approximately 50 to 65 percent will have local recurrence as a component of their disease at that time.

As you know, the risk factor for head and neck cancer include tobacco and alcohol, and this is important, particularly the tobacco use in this patient population, because of the concomitant diseases that we face, much like lung cancer. A lot of vascular disease, a lot of COPD, malnutrition from difficulty eating.

Early-stage disease is best managed with radiation and surgery. Relapses are still seen not uncommonly. Late-stage disease, really, we're talking about radiation and chemotherapy, with perhaps some form of surgery for some of these patients, but relapse remains a problem, and local relapse is still a problem in this disease.

The current chemotherapy standard that is recognized by the groups is cisplatinum/5-FU, which has been around for a while, and in the phase III setting, gives us response rates of about 30 to 35 percent, mostly partial remissions. Several new regimens are being explored in the primary treatment of this disease, but have

yet to be compared to platinum/5-FU. We should remember that most all of the studies have shown that when you have locally recurrent disease in an irradiated and surgical field, the responsiveness to chemotherapy is diminished.

Let's now concentrate on locally recurrent head and neck cancer, the topic today. This is a highly debilitating disease, as you've heard from our patients that spoke earlier. Intractable pain is not infrequent. Compromised airway from the tumor obstructing the trachea, swallowing difficulties, frequently these patients have ulcerated wounds that are quite noticeable when you first walk in the room to see them and keep them from being around people. Local problems in this disease may predominate, even in those patients with systemic metastatic disease. Median survival in this group of patients is short and their quality of life is poor.

What are unmet needs now in locally recurrent disease? In patients who have failed radiation therapy and surgery, re-irradiation is now being explored in some patients, and indeed, some promising results are being seen, but this is not an option that's open for every patient. In chemotherapy-failed patients, in primarily cisplatinum-filed patients, we don't have any approved drugs. There are multiple drugs that have activity, and multiple combinations that have been reported in the

literature. Little impact, however, overall on survival in this setting.

We need new agents with better or unique activity, with reduced toxicity, improving our palliative goals for these patients, and we need to be able to reduce the risk of catastrophic events -- airway compromise, swallowing difficulties, bleeding -- in this group of patients.

What are we talking about today? Let me show an example of a few patients, and these are patients you will hear about on this trial.

This patient had an 8 cubic centimeter tumor, lateral to the tracheostomy, and you can see the tumor right here, a small part of it, pushing into the tracheostomy, impinging his airway. He was no longer able to get his tracheostomy tube in place. His airway potentially is going to be compromised.

Here is a patient with a 4 cubic centimeter tumor at the base of the tongue, barely able to see the uvula in this patient. It is beginning to cause a significant oral problem. This is the type of problem that we're talking about today.

Dr. Howell will now talk about the pharmacological rationale.

DR. HOWELL: Let me start by being clear about

the patient population which we think is appropriate for treatment with CDDP/epi gel. And note that the indication has been refined since the NDA filing.

First, when head and neck carcinoma recurs, all patients should be considered for additional surgery, systemic chemotherapy, or re-irradiation. CDDP/epi gel is indicated for patients with locally dominant problematic lesions, who are not surgical candidates, because lesions are not resectable, resection would destroy function of a critical organ or the surgical risk is too high; who are not candidates for systemic chemotherapy because they failed prior regimens or have co-morbid disease that prohibit it; are not candidates for re-irradiation because the risk is too high, or they don't have access to appropriate radiation expertise or facilities; or who have refused all other modalities.

I would point out that this is a very small subset of all patients with head and neck cancer, and that this is an orphan indication and orphan status has already been granted for this product.

Now, the product consists of a viscous injectable gel containing cisplatin and epinephrine. The cisplatin is present as an insoluble suspension at 4 milligrams per milliliter, and of course this drug already has an established role in the treatment of head and neck

carcinoma. The epinephrine is present at .1 milligram per milliliter, and it provides local vasoconstriction in and around the tumor. The gel ensures physically stable dispersion of the cisplatin, and facilitates accurate placement of the drug.

Now, when we give cisplatin intravenously, we produce very high concentrations in the plasma compartment, and quite large overall exposures for this compartment. Some of that drug crosses into the tumor compartment, but the levels that we achieve in the tumor are quite modest, and the overall exposure for the tumor is quite limited.

What they're attempting to do with intratumoral therapy is produce very much higher concentrations and exposures for the tumor and, at the same time, decreasing the exposures for the systemic circulation. So, when we inject CDDP/epi gel at this extremely high concentration, that portion of the tumor accessed by the injection has a very high exposure. Because of the vasoconstriction, the rate at which the drug leaks out of the tumor is markedly reduced, and reasonably matches the rate at which it's cleared from the systemic circulation, so the peak concentrations in the plasma are never very high, and neither is overall exposure.

The median dose of cisplatin administered intratumorally in these studies was only 10 milligrams per

meter squared. This contrasts with the standard dose of cisplatin of anywhere between 70 and 100 milligrams per meter squared if given intravenously.

Now, there is large body of preclinical data from experimental models indicating that, in terms of local control, one can do far better by injecting this material directly into the tumor than one can do with any dose of cisplatin given systemically, even maximum tolerated or lethal doses. And if you inject intravenous cisplatin into a mouse who has a tumor here in its flank and image the radioactive cisplatin externally, you can see that there's a very small accumulation of cisplatin, and it washes out of the tumor very quickly by 1 hour. If you inject cisplatin solution directly into the tumor, you get higher concentrations, but again, it washes out of the tumor quite rapidly.

If you inject cisplatin in the form of CDDP/epi gel into the tumor, you get very much higher local concentrations, and the drug washes out of the tumor very much more slowly. This is shown in this graph. The blue line is free cisplatin injected into the tumor, short half-life. The red line is CDDP/epi gel injected into the tumor. Much higher peak concentrations, and a much, much longer half-life of the drug in the tumor.

Now, I want to point out that one of the

important versatilities of this technology is that you do not have to get good drug distribution on any one injection. This is depicted here with the tumor being shown in light blue, the gel being shown in the platinum color, and the portion of the tumor successfully accessed by drug exiting from the gel being shown in yellow.

On the first treatment, you might very well get only a portion of that tumor covered. When you treat the patient again, that tumor has undergone some necrosis and reduction in size. There is a proportional reduction in dose, but now overall you get better drug distribution. By the third, fourth and fifth treatments, that distribution has progressively improved. So, I want to point out again, you do not have to get excellent drug distribution on any one treatment for the program to be successful.

The recommended dose is .25 milliliters per cubic centimeters of tumor volume, with a maximum amount at any one treatment setting being 40 milligrams, so this is a volume per volume dosing scheme.

Now, the company faced a number of challenges in designing and executing these trials. The study was originally designed with the primary endpoint being the response rate of the most troublesome tumor. The company was fully aware from the very beginning that it was important to demonstrate clinical benefit of this product,

and in an effort to do so, clinical benefit information was collected by measuring improvement in symptoms and by looking at prevention of catastrophic anticipated complications.

The trials were powered on the MTT response rate because back in 1994 when these were designed, there was no validated method for assessing the anticipated clinical benefits of a local control.

In the years since then, all of us have paid a lot more attention to clinical benefit in terms of the importance for drug approval, and the FDA eventually asked the company to analyze for the variable patient benefit as an additional primary endpoint to this trial.

Now, that posed a problem because the trials have been powered on the basis of MTT response rate, and as noted by the medical reviewer himself, these patients have multiple different kinds of symptoms so that it's impossible to approve enough patients with any one type of symptom to properly power a trial.

And therefore, at the time this request came through, it was clear to the company that an integrated analysis of the two trials together was going to be necessary to respond to this challenge, and that analysis you will see today.

Now, there are some real problems in trying to

assess clinical benefit in this patient population. One of the problems is the enormous heterogeneity of symptoms. These patients have many different kinds of symptoms. One patient will have pain as the predominant problem, another patient will have ulceration of a wound as the predominant problem.

There is variation in the number of symptoms per patient. Some patients have a single dominant symptom, other patients have four or five problems depending on the location, size of the tumor.

Some symptoms are more important to the patient than other symptoms.

We have the problem of assessing palliation versus prevention. In the management of this disease, both palliation of the patient symptoms and prevention of anticipated devastating complications, such as invasion of the carotid, invasion of the trachea, the orbit, are important aspects of patient management.

It would be preferable to have a dichotomous variable that gave a yes/no answer to the question of whether the patient benefit had been attained, but how do you combine together measures of palliation and prevention? These are different in nature. They are measured on different scales.

How do you deal with a situation where the most

critical symptom gets better but others worsen?

How do you deal with a situation where you need to adjust palliative scores for differences in the importance of that symptom to the patient?

Well, let me remind you of clinical reality. The clinical reality is that it is very hard to achieve any kind of improvement in these refractory, recurrent, far advanced patients, as is shown here. And virtually any degree of symptom improvement is something that we in the medical community ought to celebrate.

Well, what approaches were taken in these trials to assess clinical benefit? Well, one of the things that was looked to was tumor shrinkage itself. Tumor shrinkage is often an obvious benefit, both to the patient and the physician, particularly when the lesion is an obstructing lesion. I would submit that the value of shrinking these kinds of tumor masses is fundamentally different from the value of shrinking a distal skin metastasis due to, say, melanoma or breast cancer, and that shrinkage of a tumor in these kinds of patients is a direct measure of clinical benefit.

The second measure of clinical benefit in these trials was palliation, and this was approached by identifying the patient's most troublesome tumor, and then the thing that was the most important symptom being

generated by that tumor, and then using 4-point scales to track progress toward the goals prospectively and independently selected by the physician and the patient. And I want to emphasize that both the patient and the physician selected palliative goals.

Finally, prevention was looked to. The protocol identified the critical structures that were most threatened and then measured success in avoiding the anticipated complication.

And finally, a patient benefit algorithm was developed in an attempt to try to provide a yes/no answer as to whether clinical benefit was obtained when considering both palliative and preventive goals together.

I want to be clear that every time in this presentation that we refer to patient benefit, we are talking about the calculated product of the algorithm. When we talk about clinical benefit, we're talking about all the elements that might be construed as indicating that the patient had improved with therapy.

Let me turn the podium back to Dr. Richard Leavitt, who will present the clinical trial results.

DR. LEAVITT: Good afternoon. I'm Richard Leavitt. I'm here to represent these clinical studies for Matrix Pharmaceutical, and it's my pleasure to present these results to you.

These studies were two adequate, well-controlled, double-blind and placebo-controlled trials done in patients with advanced cancer of the head and neck. The design of these studies was to randomize patients between receiving a blinded treatment with cisplatinum/epinephrine gel or placebo. It was an unbalanced randomization with twice as many patients receiving cisplatinum/epinephrine gel.

Patients were treated weekly for 6 weeks in an 8-week period. They were evaluated for response. Patients who had persistent tumor at the end of that period, or patients who had progressive tumor at any time during the therapy following three treatments had the opportunity to switch over to an unblinded therapy with cisplatinum/epinephrine gel. I would emphasize that at no time during this study was the identity of the therapy revealed to the patient, the investigator, or to the staff at Matrix Pharmaceutical.

These studies were done, one in North America and one in Europe and Israel. The studies were of identical design, followed identical protocols, and used identical patient and data collection instruments. All analyses that we will show you are intent-to-treat analyses, and the studies were simultaneously unblinded, so there was no opportunity for the results of one study to

influence the conduct of the other.

I will first present to you the efficacy analyses, including the prior treatments that patients had before receiving therapy, and then return to the question of patient benefit. And finally, to consider safety issues.

In these studies, these were patients with advanced disease, and at the time of relapse, they were all considered first for standard therapy. You've heard that we've designated one tumor, the MTT, or most troublesome tumor, as the tumor that was either most symptomatic or most threatening, and for these patients, 89 percent of those tumors had occurred and recurred in a previously radiated field. This limits opportunity for repeat irradiation, which would be the other treatment modality for local control in previously unirradiated tumors.

I'd also emphasize that 89 percent of these patients had received multiple previous therapies, including surgery, radiation, and chemotherapy, in various combinations, many at the time of relapse following primary therapy.

These are the results of the trial. The North America study, the Europe study, and the combined results. The response rates of these tumors were gratifyingly high. In the North America study, the complete and partial

response rate, again durable for a minimum of 28 days, was 34 percent. In the Europe study, 25 percent; combined results, 29 percent. In each of these trials, this result was statistically significantly different from the response in the placebo arm that was conducted simultaneously.

I would also point out that in each of these studies in the combined analysis, complete response of the tumors was nearly twice as frequent as partial response.

Even the partial responses in the study were clear partial responses. At their maximum regression, these tumors regressed from 79 to 99 percent in the group that were classified as partial responders.

Responses were prompt, and they were durable. The median time to response on this study was 21 days. The duration of response was 78 days. And I would remind you that the way we analyzed these data is that responses were censored for duration anytime the patient went on to receive any potentially confounding therapy. 33 of the 35 responders that we're discussing remained in local response at the treated tumor at the time that they went on to receive any confounding therapy, or left study for palliative care of another sort.

Time to progression is shown here, comparing the patients who were randomized to receive cisplatinum/epinephrine gel, and those patients randomized

to receive placebo. The median time to progression was prolonged in patients who received cisplatinum/epinephrine gel, 149 days.

I explained to you that this is a placebo-controlled trial, and patients, at the time that they had progressive disease or failure to respond to therapy, had the opportunity to then cross over to open-labeled cisplatinum epinephrine gel. I'll also emphasize that at that time the blind still remained unbroken, so neither the patient nor the physician nor the sponsor had any knowledge of what treatment the patient had received.

In the group that crossed over, after having failed placebo therapy, 27 percent of these patients went on to have a response. This is nearly identical to the response rate in the combined analysis from the blinded phase. This response rate was obtained in spite of the fact that these tumors had increased during the placebo treatment from a mean size of 5.7 to 10.8 cubic centimeters at the time of crossover. Again, complete responses were more frequent than partial responses.

It's also important to examine the effect of previous therapy on the occurrence of these responses. Many of these patients had received previous platinum-based therapy with cisplatinum or carboplatin, and we asked the question, was there an effect of previous experience with

platinum-based therapies on the response rate. In the 48 patients who had received either prior cisplatinum or carboplatinum, the response rate was 29 percent, and this is identical to the group of patients who were platinum-naive.

I'm now going to turn to patient benefit and the critical importance of the patient benefit outcomes in evaluating the response to this drug and the value of this drug to patients with advanced recurrent and refractory head and neck cancer. I will discuss the instrument used to collect these data, the treatment goal questionnaire, how these data were analyzed to come up with a single clear endpoint that declared patient benefit or no patient benefit, and then finally turn to the result.

The treatment goal questionnaire is designed to assess the direct effects of benefit from local therapy. What I mean by this is that patients and investigators, prior to beginning therapy, chose prospectively their goals for treatment.

Palliative goals were frequently chosen, and these were graded on a very clear 4-point scale. The differences between levels in the scale are quite clinically distinct from one another. In order to declare a benefit or achievement of a treatment goal, it must be durable for 28 days. On the other hand, failure of a

treatment goal requires simply a worsening in the score that lasts for 7 days.

Preventive goals were also assessed in this trial, and these were important to both physicians and patients, but only physicians were given the opportunity of choosing an important goal of preventing an event that they felt was clinically imminent, and clinically important.

This approach in the treatment goals questionnaire was independently validated by the Center for Outcomes Research, and Dr. John Mackowiak, who conducted that validation, is available here for questions later if you would like more detail.

I would just like to speak to the distinctness of the different levels in these treatment goals that were put before patients, and pain control was frequently chosen as an objective. We tried to make the levels so distinct that there was not a great deal of influence from subjective factors. For a patient to go from level 4 to level 3, he must have had pain that was uncontrollable and now became controllable with strong pain medicines. The most difficult step perhaps is from level 3 to level 2. Patients who were pain dependant and needed narcotics or prescription pain medicines for relief had to be able to go from prescription medicines to over-the-counter, simple analgesics. And obviously level 1 is no longer a

requirement for pain medications.

Putting together the results of these treatment goals needed a simple approach to end up with a single dichotomous clear endpoint and judgment of patient benefit. What we did is we put together these results and looked at the physicians' and the patients' responses. And the approach was very straightforward. We only scored a patient benefit if the goal was met by both the patient and the physician, or if either the patient and the physician met a goal, at least the other investigator or patient then said, my goal at least has not worsened in any way. If either the patient or the investigator said my goal for treatment is getting worse, we counted that as no patient benefit, no matter what other palliative benefits were noted by patient or investigator on other goals noted before study. The primary goal is the key to determining patient benefit in the data I will show you.

Turning now to the achievement of patient benefit. In the studies combined, 27 percent of the patients on cisplatinum/epinephrine gel, IntraDose, achieved benefit; only 12 percent of those patients on placebo. This reached statistical significance.

In the individual studies, which I will remind you we knew were not sized sufficiently to detect a statistically significant difference in benefit, there was

nevertheless a strong trend in both studies. In the North America study, 34 percent of patients achieved patient benefit by this very strict definition; only 17 percent on placebo. Similarly, in the ex-U.S. study in Europe and Israel, 19 percent versus 9.

It's also reassuring looking at these data that when you look to patients who crossed over to receive active therapy in an open label phase, the patient benefit achieved for these patients was 41 percent, despite the fact that they had now crossed over to open label because they had not achieved a response during blinded therapy. This number is nearly identical to the combined benefit rate in patients originally randomized to blind therapy.

It's important to look at the components of the treatment goal algorithm and treatment benefit algorithm in order to gain some insight into these data. This is an analysis that we did in order to look into these data in more detail.

I'm sorry. I would quickly mention that response and patient benefit were highly correlated, and although this does not prove that there was patient benefit, again it does give us confidence that the measurement of tumor response is an important measurement of the outcome of this therapy.

Again, looking now just at the palliative

component of this study and this benefit, and looking only at the primary palliative goal, there are 13 percent of patients in active, 4 percent in placebo who achieved goal, a trend that is not statistically significant. However, if we look at any of the palliative goals prospectively chosen by the patient or the physician, this difference is statistically significant, 18 percent versus 6 percent.

We also encouraged patients and physicians to be alert for other benefits that occur during therapy, even if they involve non-prospectively chosen palliative goals. And when we look at patients who reported on case report forms during therapy, while study was blinded, any other palliative benefits, we see that overall, including these previously unforseen benefits, the overall benefit rate for palliative goals was 34 percent. This is also statistically significant.

This is associated with patient response, and if you look at either the palliative goals, any palliative goal, and these unexpected and reported benefits, all of these are highly correlated with tumor response.

I'd now like to turn to the element of the patient benefit algorithm and determination which involves prevention. In this disease, advanced head and neck cancer, prevention of serious complications is an important part of the objectives of therapy. And we collected data

on these prospectively by looking for prevention of such things as invasion of a vital structure, where this can be devastating. Airway obstruction also directly threatens life, and certainly impaired swallowing. All of these were frequently chosen preventive goals, and we believe that success in achieving these goals can be very clinically meaningful.

The organs that were chosen and specified by the investigator as the organs that were threatened and that he wished to prevent complications are listed here. For those 26 instances in which the investigator chose prevention of obstruction, it was the trachea or the airway that was most frequently chosen as the organ that was threatened. For prevention of invasion, in 31 of 50 cases it was a major blood vessel.

If we now look at the prospectively selected primary preventive goal, this is also statistically significantly associated with therapy. I will mention that with regard to preventive goals, the patients on placebo were counted as failing a preventive goal if they did not have at least 28 days of prevention.

Now, there are certainly challenges in evaluating preventive goals. Most importantly, FDA has pointed out that it is difficult to make a direct comparison between the rates in the placebo group because

the patients frequently did not complete 28 days of blinded therapy. The reason that these patients did not complete therapy is the tumors were rapidly progressing, and during the time that they were on blinded therapy, the mean size of tumors nearly doubled from 5.7 to 10.8 cubic centimeters, and it is true that there were few patients available to remain in therapy at the end of 28 days. So, we must estimate what the preventive rate goal failure would be by a combination of overt failure of the goal and recognizing that these tumors were advancing and patients could not remain on blinded therapy.

Finally, we would propose that including preventive goals is important in assessing patient benefit. There was a single patient benefit outcome that was prespecified for both palliative and preventive goals. Physicians do believe that prevention is crucial in this disease, and in one respect, the ability to actually complete the 8-week blinded therapy is implicit evidence of important attainment of prevention. All of this was part of a prospectively planned analysis. It is important, once the blind is broken, to look at all of the components that might contribute to the palliation and the palliative benefit, but these kinds of analyses by both the sponsor and by FDA should be secondary and help to explain the data, but should not replace the primary analysis.

I would like to turn to other data that are supportive of these results that we have found in the clinical trial, and I would speak specifically about two open-label studies in other solid tumors, mostly in patients with tumors such as chest wall recurrence of breast cancer, malignant melanoma, sarcomas, and other tumors. The efficacy endpoints in these studies are identical to those that I showed you for the head and neck cancer trials.

Looking at the combined response rate overall, the response rate was 35 percent; 31 percent in a U.S.-North America study, 41 percent in an ex-U.S. study. Complete and partial responses were frequent.

Now, let me take you through this slide. We looked at patient benefit in these studies as well, but we did not have a simultaneous placebo control. The patient benefit rate for these studies was 37 percent and 25 percent, and again, we have confirmation from the association of benefit and response that local disease response is a meaningful outcome to measure and examine in these studies. Amongst responders, 55 percent were benefitters in the North America study, 50 percent in the ex-U.S. study. These differences are either statistically significant, or nearly so.

I'll quickly turn to the safety profile,

talking about dosing questions and the ability to deliver the expected and projected dose, selected adverse events, and specifically local cytotoxic effects, the things that we expect to happen at the site of the treated tumor that frequently accompany response. And finally, I'll briefly discuss selected clinically important adverse events.

FDA has pointed out that patients did not receive the full 0.25 milliliters per cubic centimeter of tumor determined by the original treatment volume. However, true dosing errors were actually very infrequent in this trial. In most cases there was no dosing discrepancy, and in those cases where there were changes from the ideal dose, these were most frequently due to things that were pre-specified directions in the protocol for changing the dose. For example, if injecting locally into the tumor could simply not be accommodated, then dosing was supposed to have been stopped, and it was appropriately in 11 percent of the cases that received active gel.

Another 2 percent of cases had an incomplete dose delivered because there was some of the drug that actually refluxed from the tumor.

Other dosing deviations included such things as stopping treatment when the tumor responded. Again, specified by protocol.

Reasons such as adverse events were rare. Patient refusal of therapy was rare. And there were true dosing calculation errors in only 4 percent of the cases.

Now, this is a very busy slide, but I'd like to take you through some of the adverse events that occurred during these trials. In these two columns are data for cisplatinum/epinephrine gel. Here are data for placebo. And we have divided these between mild and moderate reactions and those considered severe.

For immediate injection effects, those things that are part of the injection procedure, mild and moderate pain were of identical incidence between the patients treated with cisplatinum/epinephrine gel and those treated with placebo. Severe pain was noted more frequently, however, in patients receiving cisplatinum/epinephrine gel, 10 percent versus 4 percent in the placebo group.

Otherwise, the incidence of side effects is close in these studies, but I will point out certain substantial differences. Again, at the site of treatment, mild to moderate or severe pain that occurs during the reaction and response of the tumor was more frequent and active than placebo. And similarly, when you look at distant effects such as pain, these were equally frequent in active and placebo. It is only the local condition where there is a substantial difference in pain between the

two treatment arms.

I will also point to nausea and vomiting, which would be expected frequent complications of systemic cisplatinum therapy. These were seen somewhat more frequently, 14 percent, 14 percent, in the active, and only 5 percent and 1 percent in the placebo. This difference may have been due to low systemic levels of cisplatinum, or perhaps more likely the more frequent use of systemic narcotics.

Lastly, there are local conditions that develop at the site of recurrent tumor and at baseline, before these tumors retreated. We carefully reported all of the local conditions surrounding the tumor, and you see these listed here. And the bars are for active group and those that received placebo. And you can see these are about equal at baseline before therapy.

If we now turn our attention to any worsening of these conditions, either the developing of a new condition or the worsening in degree of any of these, there was an increase in these conditions for those patients receiving cisplatinum/epinephrine gel. Most particularly, erosion and ulceration occurred more frequently in cisplatinum/epinephrine gel, as did necrosis. However, the occurrence of eschar, which one can see as part of the healing process as tumors and local cytotoxic conditions

resolve, were virtually only seen in the patients who received cisplatinum/epinephrine gel.

Finally, there were other clinically important adverse events that occurred. We saw six patients in these studies who developed cerebrovascular events. Five of these occurred in cisplatinum-epinephrine gel group, one in the placebo group. These happened early in the trials. We carefully analyzed each of these patients and concluded, although not conclusively, that these were most likely due to carotid artery vasospasm, perhaps from needle trauma to the carotid artery or from irritation of the artery.

We changed the protocols. We excluded tumors that directly involved the carotid artery, and since doing that we have treated most of the patients in the study, and we have not seen another treatment-related cerebrovascular event.

There were some cardiovascular changes that were noted during these studies, mostly blood pressure and pulse elevations, which were prospectively measured and assessed for each patient in the study. These were transient. They were not associated with any serious adverse events. A single patient had an apparent loss of consciousness that was a possible cardiopulmonary arrest. The patient was hospitalized overnight and released the next day without sequelae.

In summary, I've shown you two adequate, well-controlled, placebo-controlled trials randomized in patients with advanced head and neck cancer. The results in these trials stand on their own, but they are also confirmatory and complementary of one another. We've shown you that effective local control can be achieved in patients with advanced recurrent head and neck cancer. These were associated with real patient benefit: palliation of symptoms, and prevention of complications. And the patient benefit is associated with tumor response. The supportive trials had high response rates in patient benefits, and overall the safety profile is well managed.

I'd like to invite Dr. Howell to return.

DR. HOWELL: As you heard, the patient benefit algorithm was an attempt to provide an assessment of both palliative and preventive goals within the same patient, but perhaps the simplest, cleanest way of looking at palliative benefit is to take the population of patients who had particular symptoms and ask what fraction of those patients got better.

This slide shows the three palliative goals that were most frequently selected, for which the numbers were large enough to make any reasonable analysis. And what you see is that on the CDDP/epi gel arm there was a modest, admittedly so, but very consistent difference in

all of the goals selected by the patient and all of the goals selected by the physician. Recall that the instruments used to measure progress toward these palliative benefits had big jumps between one level and the next, so modest attainment of improvement was expected.

Now, the FDA has performed an analysis of the attainment of primary palliative goals, and has presented the data in this table for your consideration this afternoon, for a vote on whether they provide substantial evidence of clinical benefit. And the data show that some patients get better and some patients, and a different fraction of patients, get worse. This is what we expect from the use of chemotherapy in this patient population. It's part of the natural history of the disease. This product does not cause a response rate in greater than 50 percent of the patients, so one doesn't expect a shift in the median, we don't expect all patients to improve.

Now, there are a couple of things about how this data was calculated that are important for you to understand. In order to score as better, the improvement had to last for a full 28 days. In order to be scored as worse, the worsening only had to last for 7 days. This was a purposefully conservative scoring system. If an improvement doesn't last 28 days, you know, its value is not so clear. But if something gets worse, even for 7

days, that can really impact on a patient's well-being.

Now, the default is that we expect more patients to worsen in this situation than to get better, and we also expect, because we know that CDDP/epi gel causes transient local symptomatology due to tumor necrosis, to produce some transient worsening in some patients, particularly patients in whom the tumor invades the skin overlying the tumor mass.

Now, the second thing that's important for you to understand about this data is that patients stayed on the CDDP/epi gel longer than on the placebo arm, so there is a greater chance of worsening in the CDDP/epi gel arm.

Now, the FDA folks have raised the question as to whether treatment with CDDP/epi gel makes these patients worse. And if you take exactly the same data and now you look at just the first 28 days, because that's the period when the largest number of patients on both arms of the study were still on study, and you score improvement and worsening on the same time interval, 7 days, then you get this set of data, and there's a consistent small effect of CDDP/epi gel over placebo in both studies and in the combined data.

Now, some patients are still getting worse. But if you look at the data over a time period of the full six treatments and the 1 month of follow-up, over the time

period when we expect the local effects to have largely resolved, you see absolutely no evidence that there's a difference in the worsening rate between the two arms of the study. In fact, if you look at the obstructive symptomatology, there's a substantial concern that the patients on the placebo arm are getting into trouble with obstruction at a higher rate than the patients on the CDDP/epi gel arm.

But now, maybe the most important way to look at clinical benefit in this patient population is to ask, look, if a patient attains some benefit, is there any possibility that that benefit is offset by something else going wrong in the same patient? So, 12 percent of the patients in these studies attained either the patient's or the physician's primary palliative goal. Now, if we take away from that any patients whose other primary goal worsened, we wind up with a net primary palliative goal rate.

Now, there were no such patients in these trials, so we see a small positive event. This is a patient population where we can be really pretty sure that clinical benefit was attained because of a good correspondence between the physician's evaluation and the patient's evaluation.

Now, if we do exactly the same thing with

respect to all palliative goals, 18 percent of patients attained - I'm sorry any palliative goal, either primary or secondary palliative goal, and take away those in which in the same patient something worsened -- that occurred in 4 of these patients -- we wind up with a benefit in terms of palliative goals of 14 percent. Again, a pretty high confidence level that this is a population of patients who really have benefitted from this treatment.

So, what are the pieces of evidence that speak to the issue of clinical benefit from these trials? Well, first is the fact that there was a statistically significant difference in response rate in both studies, and in some of these patients, particularly those with obstruction, this represents an obvious clinical benefit. And such a response rate is, as a separate issue, reasonably likely to predict patient benefit.

There's a positive trend for the patient benefit variable calculated by the algorithm in both studies that reached statistical significance in the prospective integrative analysis. When examining palliation, there's improvement, small, but there for each type of symptom when examined individually.

In the integrated analysis of all primary and secondary palliative goals -- these are the palliative goals only -- there was statistical significance. And if

you add in primary, secondary and the unforeseen benefits that reached statistical significance in each trial individually, studies 403 and 503, the phase II trials, provide supportive evidence that this drug is active and that it provides patient benefit.

Now, let me pose a rhetorical question. What level of certainty do we need on clinical benefit in a population of patients who are very narrowly defined, have a devastating problem, and no other therapeutic options? I would submit that the evidence available from these trials is reasonably strong, provides a reasonable body of evidence that this product is effective.

Dr. Mills.

DR. MILLS: Thank you, Dr. Howell.

I'll be brief in the summary.

I think, looking at risk/benefit at the end, I'd first like to say, what are the risks and benefits of the current therapy we have for this patient population? And obviously no therapy is going to be an option for many of these patients, and I think we do know what will happen. These patients will get worse. Local problems will progress with bleeding or airway obstruction. There will be a decline in quality of life, and some of these critical local tumors may shorten the patient's life.

Current therapies, radiation therapy, re-

irradiation can be tried, but frequently we have an ineffective dose in this patient population. Surgery is usually not an option. Chemotherapy, we have to be careful. I think if we recall from Dr. Forastiere's paper in April JCO, this is a particularly fragile population, prone to toxicity. And there's little improvement in survival with any of our options at the present time.

Cisplatinum/epi gel I believe has been shown to have few serious side effects. They are usually local wound care and can be managed. Systemic effects were uncommon. I think strokes did occur, but with appropriate patient selection to avoid tumors that involve the carotid artery, this can be avoided.

The benefits. Well, we do have a high complete response rate in this trial, and that I think is an intrinsic benefit for many of these patients.

Clinical benefit was seen, both palliative and preventive, and one good thing is these responses were prompt, 21 days, meaning you could use this product and move on to other treatments in a relatively short order of time if you needed to. My patients, I gave it outpatient to all of them. It was an outpatient procedure and it was not difficult.

What about the patients we discussed earlier? Our first patient had an obstructing tracheal lesion, right

here. Here you can see after therapy with cisplatinum/epinephrine gel, the tumor has responded. He eventually did have a tumor response and you see the eschar formation. I think you've heard from his son that he benefitted.

Our patient with the oral tumor had a complete response, a complete resolution of their tumor with therapy.

I do believe that this gives these patients a third form of local therapy to be considered in their management. It gives me a needed addition that I need in the clinic to help these people when local problems are the predominant problem and we have nothing else to offer. It is an effective and beneficial therapy for local disease.

Thank you.

DR. NERENSTONE: We will open up the questions to the sponsor from the committee. Dr. Kelsen?

DR. KELSEN: Could you describe to us how you validated this quality of life instrument, and in particular, for example, for pain control, could you describe how you determined that moving from level 1 to 2 was significant. Was this compared to MPAC or to other instruments which are felt to be validated?

DR. MACKOWIAK: Yes. My name is John Mackowiak, Director of Research at the Center for Outcomes

Research in Chapel Hill, and I personally conducted that validation.

Slide 287 on, please. We did a number of things to validate that instrument, and the results were that we found that it had excellent validity, good reliability, and clinical meaningfulness, and I'll summarize those.

In the validity aspect, I interviewed patients with head and neck cancer, as well as investigators who participated in the trial. I learned that all of them agreed that the instrument had excellent content validity. We had the right items in the questionnaire. And from the study results, we know there was high association between tumor response and the benefit endpoints. We also know there was good reliability, but most important, there were important clinical differences.

Can I have slide 614, please? In interviewing patients and investigators both, I showed them these four different levels of pain control, which you saw earlier. And they had to sort them in the correct order first. They had their own independent cards. After sorting them in the correct order, I asked them the simple question, is it clinically meaningful to move from level 4 to level 3, is it clinically meaningful to move from level 3 to level 2, and on?

There were eight different questions, three questions on each one, and from the physicians, almost 100 percent of physicians agree that all these levels were clinically meaningful. Some of them were slightly less meaningful. Patients, all of them, agreed 100 percent of the time that the levels were clinically meaningful. So, that was how the validation process was done.

DR. NERENSTONE: Dr. Redman.

DR. REDMAN: Several questions again on the endpoints. Looking at your scale and specifically pain, if a patient required increasing narcotics for pain control, they wouldn't leave level 3. How did you score that?

DR. HOWELL: You're correct. If they did not have a dramatic reduction --

DR. REDMAN: I'm not talking reduction. I'm talking increase. Negative benefit. Patients on narcotics for pain control while on study requires increasing doses of narcotics. They're still level three.

DR. HOWELL: Yes, that is exactly true. You identified one of the issues with this instrument. If the patient required increasing levels of narcotics but still managed their pain, they stayed on level 3. In addition, if their narcotics were cut in half, 50 percent reduction, as was true with gemcitabine with their clinical benefit response claim, they still stayed on level 3. Even if they

stopped using narcotics but switched to another prescription medication, they stayed on level 3. So, we know that the instrument is very valid.

If they do achieve a change in one level, we know there's a clinical benefit, but we also know now after using it, that it's not sensitive to some changes. Even though they may be achieving benefit, the instrument doesn't pick that up.

DR. REDMAN: A similar question for clarification. The patients identified their palliative endpoints on day 0, before treatment. If one of those endpoints was not pain control -- in other words, the patient put a level 1, I'm not having any pain, so you didn't consider that an endpoint. The patients on follow-up were only asked to assess those palliative points that they identified at the beginning, so if some other new symptom developed but they didn't identify it at the beginning, it was not recorded? This is for clarification.

DR. LEAVITT: Yes. I want to make it clear that on quality of life data, those were all prospectively chosen goals. However, anything that happened that made the patient worsen would have been reported as an adverse event. And for example, I showed you very briefly the adverse event data on the pain associated with the procedure in the immediate post-injection period. So, all

of those would show up in our adverse event recording, but might not have had an impact on moving somebody up if they were already at the maximum goal. Maximum level.

Does that answer your question?

DR. REDMAN: Not quite. I think it's just clarification. A patient identifies four palliative factors that have a numerical value greater than 1 to them, but while on treatment, a factor that they didn't identify at the beginning becomes important to them. I think, at least the way I read it, they were asked to evaluate only the points they picked out at the beginning.

DR. LEAVITT: That's correct.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Yes, thank you. I have three questions.

How consistent, and what evidence do you have that your tumor volume measurements between injections and between centers, and which is really quite critical for the pharmacokinetics and the dosing, were consistent?

DR. HOWELL: The volume measurements were reasonably consistent. Recall that all the patients who were candidates for this trial had easily measurable lesions. They were preselected to be patients whose lesions could be easily measured. And there was a high reliability index in terms of being able to monitor changes

in tumor volume, particularly under circumstances where a very large fraction of these patients actually attained not only CR but also a very, very good PR.

CT-scans were used often to look at the anatomy of the tumor, and sometimes to provide the depth measurement, but you recall that highly accurate measurements of tumor volume during this treatment phase are not really required for treatment success. You get good drug distribution, variable but good drug distribution, in the tumor by virtue of the opportunity to treat again and again, and precise dosing is neither required nor operationally clinically feasible in a wide variety of tumors. There's so much tumor heterogeneity that you basically have to do the best you can, as you would if you were infiltrating with lidocaine or another local anesthetic.

DR. BLAYNEY: And that is the second question. One of the photos you presented in your briefing document here, the poor fellow with the enucleation of his eye, you measured an MTT, most troubling tumor, that has an arrow pointing to it. A lesion in that eye socket that's superior looks like it waxes and wanes. If you had pointed the arrow toward that tumor, that could have been a complete response, is the way I view these photographs.

DR. HOWELL: That's a difficult photograph.

Let me ask Dr. Elias to point that out exactly to you.

DR. ELIAS: I'm Dr. Laurence Elias, Medical Director with Matrix Pharmaceutical.

Why don't we go ahead and look at the slide of the patient you're referring to. Let me just walk you through this. This patient's most troublesome tumor was in this area here, and on placebo this grew. Then when the patient was crossed over to active treatment and had a good response of the MTT. Later there was a tumor superiorly, but the protocol permitted a treatment of tumors other than the MTT, and this was also treated and responded.

DR. BLAYNEY: You're talking about the lesion at the level of his helix there?

DR. ELIAS: Excuse me?

DR. BLAYNEY: The lesion at the level of his helix.

DR. ELIAS: I don't believe so. These are difficult lesions to photograph. We did not use these photographs for evaluating response, but are presenting them illustratively and use them to identify the MTT for the benefit of the investigators.

DR. BLAYNEY: My point is, though, it's very difficult to - even the MTT tumors, if you'd have picked some that weren't necessarily injected, that you could have had responses just on the basis of happenstance, perhaps,

or blood growth, or tumors falling off. I agree with you, these are difficult to measure.

DR. ELIAS: If we could have the next slide on. Again, the measurements were all done in the clinic by experienced investigators, and this is what really determined the responses we're reporting. And these pictures are illustrative.

But here is another patient who had an MTT that you can clearly see at the base of the neck, clearly in a threatening position. Now, this is a 44-year-old man who had originally a primary tumor at the base of the tongue, subsequently had multiple surgeries, radiation therapy, had several courses of cisplatinum/5-FU. If you go through his history, he was a convincingly refractory.

This patient went through the typical sequence of tumor necrosis, shown here at day 43 on treatment with cisplatinum/epinephrine gel, and then went on to have a very nice response with very nice healing at this point.

DR. BLAYNEY: And perhaps my last question is, it's very difficult for me to understand or to say that the gel is not a way of delivering epinephrine locally in a low dose of weekly cisplatinum and may have gotten the same tumor response, since you didn't do a control with epinephrine and your matrix material, your collagen material.

DR. ELIAS: Well, I think you can appreciate the difficulty of clinically doing multiple different types of placebo treatment, but I think the answer to your question is well addressed by some of the preclinical data we can show you.

DR. HOWELL: Actually, it sounds like your concern was the question of whether if one had just treated with epinephrine gel, whether one would have seen these same kinds of dramatic --

DR. BLAYNEY: Local epinephrine is painful, produces necrosis.

DR. HOWELL: Let me ask, would you expect that the injection of epinephrine to be able to manage this kind of lesion, substantial lesion here in the throat? Would epinephrine have been capable of winding up with a tumor reduction? I think most of us would think probably epinephrine alone couldn't have done this. Your point is well taken, and there was a very substantial debate about whether epinephrine should be included in the gel.

One has to be careful in selecting a placebo, that it doesn't cause patient problems. And epinephrine had the potential to do that.

DR. NERENSTONE: Dr. Lippman.

DR. LIPPMAN: I just had a few questions to get at the issue of the magnitude of the response and things

that can affect this because as I understand it, most of the tumors were measured -- and it would be nice to see the data -- by clinical measurements. It would be good to see the data in terms of response by CT.

But the question I was getting at is the issue of being able to maintain the blind. In the document you indicate that the color of the active gel was different than the color of the placebo gel, and that it was put in a syringe to try to mask the difference. I guess the concern I have hearing the presentation is that the major problem that you couldn't get the drug to people is because the drug leaked, for lack of a better word. So, the drug came out. That was the major problem for not giving adequate therapy. If the gel is really a different color, it would be difficult to maintain the blind. And if the blind can't be maintained and the measurements are subjective, it makes it more difficult to determine the magnitude of the activity.

DR. HOWELL: Two points on that. You are right, there is a slight difference in color, and when the drug refluxes from a tumor that you've injected, it's usually mixed with blood, and that completely eliminates the color difference.

Let me ask Dr. Glenn Mills, who's had a lot of personal experience with this, to address that issue.

DR. MILLS: Yes, Dr. Lippman, there is a slight color difference between the gel and the placebo. I think if you put this on a white piece of paper you can clearly see the difference. But you know, with these tumors like you've seen, when you're injecting them and you get a little reflux, I found it very difficult to tell a color difference, if any, in my patients because of that admixture, some of the necrotic tumor, as well as some blood in it. I don't really feel like I could tell a difference.

DR. LIPPMAN: It didn't indicate what color it was. I just wanted to see how confident you were about maintaining the blind.

The other issue I have reflects sort of the dose response data. So, there was no difference in response rate at the higher versus the lower dose, but in fact I guess one aspect about that is that I was a little surprised that there was no difference in toxicity. I was having trouble finding the table, but there was significantly more nausea, I think, in the treatment group overall, and one might have expected that nausea would have been higher with the higher dose. So, I'd like your thoughts on that.

And the other issue of dose response in terms of activity -- again, there's no difference in the two

doses that were used, but in fact, when one looks at the two pivotal trials, the one that looks most promising is the 414, which had a 34 percent response rate, a median duration of 85 days. The other study had a 25 percent response rate and a median duration of response of 64 days.

Yet, the 414 with the best results had the lowest compliance. In fact, that was really one of the major differences between the two studies, as I saw it, that particularly the group randomized to the IntraDose, 47 percent were able to take 80 percent or more of the drug. That's table 29, I believe, on page 46.

So, I'd appreciate your thoughts about these issues with dose response and dose that actually was received.

DR. HOWELL: Let me make just one point to start the answer to you. Remember that in local tumor therapy doubling the dose does not double the response rate, and you wouldn't expect it to. Doubling the dose does not get twice as much drug distribution within a local tumor nodule. So, the kinds of relationships between dose and biologic effect that we're used to dealing with in the intravenous world are different in a tumor, where we don't have such a rigorous and tight relationship between the dose actually gotten into the tumor and the response, because we don't always get the same distribution.

Let me ask Dr. Leavitt to address that point further.

DR. LEAVITT: That's correct. The question is, was there a change in response rate? The benefit rate and the response rate was maintained before and after the change in dose, and what you can see is in the 414 study the benefit rate was 42 percent. It dropped to 29 percent afterwards. The 514 is 24, 17 percent.

DR. LIPPMAN: So, there was a lowering of response rate, but not significant with those small numbers?

DR. LEAVITT: That's correct, and if you look here at response rate, you can see that the overall response rate went from 29 to 37 in the North America study, 29 to 22 in the ex-U.S. study. Overall, the 29 percent was maintained, and there's no difference statistically between these.

DR. LIPPMAN: And I wondered, do you have the response data from the combined studies with CT measured tumors? Do you have that available?

DR. HOWELL: No. CT scans were not used to assess the response in these studies. I would just point out that some of the cooperative groups have now ceased and desisted using imaging technology to assess the tumor response because of the complications of trying to image in

irradiated fields and so forth.

DR. LIPPMAN: Just one final question. Do you have the data available, in terms of response data and the combined studies, on patients who failed cisplatin for recurrent disease?

DR. HOWELL: Yes, we do. Dr. Leavitt?

DR. LEAVITT: What we have are response rates in patients who have had previous exposure to cisplatin or carboplatin. Those are not always patients who had an immediate proximate failure of platinum. Some of those patients had had cisplatinum as part of initial management, and if you consider recurrence after initial management with adjuvant chemotherapy, then that's a failure.

Turning here, you can see amongst those patients who had either cisplatin or carboplatin -- and most of these, by the way, are cisplatinum -- 29 percent, 30 percent for those who are platinum naive.

DR. LIPPMAN: Sorry if I didn't clarify the question. I was looking specifically at patients who had failed cisplatinum for the management of recurrent disease, since there may be a difference in patients who receive, for instance, neo-adjuvant therapy had prolonged disease-free intervals and then recurred. Do you have the data by use of cisplatinum for the management of recurrent disease, then going on to this study?

DR. LEAVITT: I can get those data for you, I think, but I don't have those at my fingertips.

DR. NERENSTONE: Dr. Sledge.

DR. SLEDGE: A number of questions. First, with regard to inclusion and exclusion criteria, which are with regard to the universe of patients that we're talking about, I'm trying to get some sense of who actually is being treated here amongst all patients with recurrent head and neck cancer. On slide 6, I think it says that there is 7,500 to 10,000 patients a year with local disease who go on to die of head and neck cancer.

What's the real universe here, though, if we exclude patients with tumors greater than 20 centimeters squared, anyone with carotid involvement, anyone with carotid vascular disease, which I've got to imagine is reasonably common in this patient population, and anyone with systemic disease? What actual numbers are we talking about here?

DR. HOWELL: Let me ask Dr. Everett Vokes to address that issue.

DR. VOKES: I think that this would be a small number of patients, since those who have recurrent disease would first be considered for radiation; if they haven't had that, for surgery or chemotherapy. And you are excluding those patients with large bulky masses or those

where carotid involvement cannot be excluded. So, I think it is a small number of patients. I could not give you a number for this nationally. I would estimate that it's maybe 2,000, 3,000.

DR. SLEDGE: So, 20 to 30 percent of the whole, roughly speaking?

DR. VOKES: At some point during their treatment.

DR. SLEDGE: When I look at the end of the briefing book, where it talks about the indications for the drug, most of these exclusion criteria are not mentioned. Does the company intend to ask for an indication that includes all the exclusion criteria used here?

DR. HOWELL: Yes. As I indicated, the indication has been refined since the NDA was submitted, so it's refined from what is printed on your question sheet today, and that is, we're talking about the patient population who are not candidates for surgery, not candidates for systemic chemotherapy, not candidates for re-irradiation, or simply have refused all of these things. So, it is a very small, narrowly defined patient population.

DR. SLEDGE: On slide 50, where you have the adverse events reported in greater than 8 percent of patients, for those of us who don't add very well, can you

give me some sense of the total percentage of patients having grade 3 or 4 toxicity on the treatment arm versus the control arm? Total percentage. Not total number of patients, but total percentage of patients with grade 3 or 4 toxicity.

DR. ELIAS: The severe toxicities were relatively rare. Not seeing the data totaled in exactly the way you're asking for, but please note we can go ahead and look at that table again, that severe toxicities were relatively rare.

DR. SLEDGE: I ask because they seem to be more common in the treatment arm than in the control arm.

DR. ELIAS: They certainly are. The most common toxicity is pain, and all pain in all categories -- I think your question is about summing across several categories. Pain in all of these categories comes up to roughly 60 percent of patients, all grade.

DR. SLEDGE: It seems to me to be more than just pain.

DR. ELIAS: Any episode of pain during the entire course on observation, on study in blinded phase.

DR. SLEDGE: It seems to me that in just about every category there's more in the treatment arm than in the control arm. So, I'm trying to get some sense of the total number of patients, total percentage of patients who

experience a severe side effect.

DR. ELIAS: We don't have it summed in exactly that way, but we do acknowledge that there are side effects and toxicity with this, as with any other treatment or medication, and that as I've just pointed out, the most common toxicity is pain, which could occur as a local immediate injection pain, as a pain in the local area, or a systemic pain in some other area. But this occurred more frequently in the treated group than in the control group, but it was not terribly common.

DR. HOWELL: Dr. Sledge, maybe it would be useful to hear directly from one of the investigators about whether pain or any of the other symptoms were particularly severe. Let me ask Dr. Glenn Mills again to address that issue.

DR. SLEDGE: You don't have to do that. I'm just saying, using what you call severe.

DR. HOWELL: Sure. The numbers are slightly different but they're not big differences, and we know that this is a product that causes -- and purposely we want it to cause -- local necrosis and some pain in that area.

DR. SLEDGE: But a lot of the side effects listed as severe appear to be systemic side effects to me.

DR. HOWELL: I think if you look down the list of systemic side effects, the event rates are low and the

differences in the event rates are pretty modest.

DR. SLEDGE: But I'm asking in toto, since in just about every case, it appears to be more in one than in the other.

DR. HOWELL: I apologize. We simply don't have it available here now for that analysis.

DR. SLEDGE: Finally, for those of us who live in a centimeter squared universe, as opposed to the centimeters cubed universe, how do you measure centimeters cubed in these patients?

DR. MILLS: Well, I'm not a mathematician either, but the formula that Matrix supplied for us to calculate they tell me was based on a spheroid, which is length, width, height, times one-half. That's basically how you determine the volume determination.

DR. SLEDGE: When this gets into the clinic with the general medical oncologist, do you think that will be an easy switch?

DR. MILLS: I think for this product, yes, because it's a volume calculation and it's a volume per volume dosing. It's not a dosing based on creatinine or white count. So, you have to figure the approximate volume that you need. And I think that's good because when you treat these tumors, you do get an idea when you're injecting them whether you're getting good coverage because

the gel does swell the tumor a little bit and you can see where you've injected.

DR. SLEDGE: I'm not saying it's bad. It may be the right way to do it for all tumors. What I'm asking is that if you were a clinician who sees 5 or 10 of these patients a year and are not used to the measurement method and you're giving a dose which is based upon the volume of tumor, what I'm asking is, do you think this will be an easy switch.

DR. MILLS: I think it would be an easy switch. It wasn't that difficult.

DR. NERENSTONE: I'm going to take the chair's prerogative for two quick follow-up questions to Dr. Sledge. Because you are basing a lot of this on clinical benefit, what about the duration of the toxicity? Do you have a slide about that?

DR. HOWELL: Let me give you a quick answer to that while they're getting the material. The local necrosis affects the swelling. The erythema resolves usually over a period of 20 to 40 days, sometimes taking slightly longer in some patients, but it is a fairly predictable, clear process of erythema inflammation followed by healing.

DR. NERENSTONE: At what point then do you calculate your duration of response? Because your duration

of response median is 70 days. So, do you have the duration of response after the 40 days, or is it at the time of first change of the tumor?

DR. LEAVITT: Response duration was calculated very directly from the time of first onset of response, at least a 50 percent decrease in tumor, to the time of relapse.

DR. NERENSTONE: So, part of the 70 days duration could be at a time when patients are having more pain because it takes 40 days for the tumor pain to go away.

DR. LEAVITT: That's correct.

DR. NERENSTONE: And the second question, just a clarification. Dr. Sledge said something about systemic disease. My understanding is that systemic disease did not preclude enrollment on this trial. Is that correct?

DR. LEAVITT: That's correct. Patients had to have local dominant disease, and patients had other distant metastases that were symptomatically dominant, they should have gone on to receive other chemotherapy if they were otherwise good candidates for it.

DR. NERENSTONE: Thank you.

Dr. Kelsen.

DR. KELSEN: You described in the briefing book why you decided to develop your own palliation scales. Did

you compare them to scales, for example, for pain, which are well described by other investigators, such as MPAC, or any other instrument that's been validated. That's question one.

And question two is, how many patients using your scale moved two levels of improvement? That is, not from I guess going down from one to two, but from two to three steps down.

DR. LEAVITT: Let ask Dr. Morgan Stewart from Matrix Pharmaceutical to address that.

DR. STEWART: I'm Morgan Stewart. I'm the Director of Biostatistics and Data Management.

To take the second question first, there actually were not a lot of patients who had a two-grade increase, or actually it was a decrease, corresponding to an improvement. As was pointed out earlier, we purposely, when we designed the instrument, made these grades distinct from each other, and it would have been very difficult, although a few patients did do it, to have a sustained for 28 days or more displacement of two grades from baseline.

DR. KELSEN: Why would it have been difficult? I would have thought a patient who has level 3 pain -- that is, has to take a prescription drug, then going to either Tylenol or aspirin or no pain. How many patients actually were able to do that? Why do you think that's so

difficult?

DR. STEWART: I believe there were three in the two studies. I'd have to look at the data to be sure. Remember that these were advanced patients.

DR. KELSEN: And did you compare this pain instrument, your pain scale, to other pain scales?

DR. STEWART: Yes. One of the other instruments that we used on these studies was the FACT head and neck scale, and that includes a pain question, asking -- I think it's a 6- or 7-point scale -- about current pain status. We looked at our patients who had selected pain as one of their goals versus what they had scored on the FACT.

Now, unfortunately, we've had a lot of problems getting patients to fill out the FACT. The compliance was low. And so we've been told by the developer of the FACT that we should interpret any data having to do with the FACT -- it's almost worthless because we had less than 50 percent of the patients who had a FACT score recorded after baseline.

So, while we did see some degree of association between patients who said that they were getting better on the treatment goal questionnaire for pain, also getting better on the FACT, it's difficult to interpret those data because of the low compliance on the FACT.

DR. KELSEN: So, could I just follow that?

That means that they did do a FACT-head and neck, as well as this instrument.

DR. STEWART: Yes.

DR. KELSEN: But you don't have data from the FACT-head and neck.

DR. STEWART: We don't have reliable data because of the low compliance.

DR. NERENSTONE: Mr. Gruett.

MR. GRUETT: Looking at your background document, the mixing of the three chemistries involved, I have a follow-up question to this also. Why can't this be done ahead of time? Why does it have to be done just prior to injection?

DR. HOWELL: I'm sorry, I'm not entirely sure. Why does the mixing have to be done?

MR. GRUETT: Have to be done ahead of time? Why does it have to be done just prior to injection?

DR. HOWELL: This product doesn't contain any preservatives of any sort, and it's not necessarily as stable as a formulation with all three components, the epinephrine, the cisplatin, and the gel mixed together, for a long period of time. So, since the drugs are easily mixed together in the syringe immediately before injection, the approach was to do it that way rather than trying to develop a product that had a shelf life where all three

things were mixed together.

Am I answering the question?

MR. GRUETT: Yes. That brings up a concern about the shelf life within the tumor and the potential of toxic breakdown of the drug within the tumor. Do you have a half-life or table showing the length of longevity the drug has before it breaks down?

DR. HOWELL: With cisplatin the pharmacokinetics are a little bit different. The product that this drug breaks down to is something that is exited from the tumor very rapidly. This drug has to get into the tumor cell, has to undergo activation inside the cell, and then reacts with the DNA. We don't expect in any clinical circumstance to see a lot of "breakdown" products that are toxic in the tumor or the plasma. There are some metabolites that have been inactivated, but we have strong evidence to indicate that the drug stays in its active form in the tumor for quite a long period of time relative to when the drug is injected just as a free solution.

MR. GRUETT: I didn't see any studies at all in your background information on this. Do you have those?

DR. HOWELL: Let me ask Dr. Robert Tressler to show you an example of the effect of the formulation on retaining the drug in the tumor.

DR. TRESSLER: If I understand your question

correctly, you want to know how the gel product was broken down?

MR. GRUETT: Yes, and what happens in the tumor. How long does it exist in its present property?

DR. TRESSLER: I don't actually have a histographic slide prepared for that, but what I can tell you is we did look at that and did do a series of preclinical studies and histologically assessed the time course of absorption and dissolution or breakdown of the collagen gel product containing cisplatin. What we showed was that intratumorally, and also in normal tissues, collagen breakdown started to occur within 7 to 14 days. And by day 30 to 60 we could no longer detect any presence of the collagen matrix in the tissue by histological examination. And we looked at a variety of tumor types over a time course.

So, we see very nice bio-absorption, if you will, without significant changes.

DR. NERENSTONE: Dr. Pelusi.

DR. PELUSI: I believe my questions will go to Dr. Mills, since I think he's had the most experience. Dr. Mills, could you describe for me the patients as they came in. Were they all done as outpatients, and did they have to stay in the town where they were treated?

DR. MILLS: All the patients that I've treated

on Matrix trials were done as an outpatient. I have a healthy respect for cisplatinum since when, I was a fellow it was the pre-dansetron days, so every one of my patients was pre-med and I had no nausea and vomiting. I gave them Demerol.

The pain that we're talking about in this procedure is the pain like in our clinic if we do a bone marrow aspirate and biopsy. It's similar to that pain. It's a transient pain, lasts a day or two, and then it's gone. It's not a real long-lasting pain.

If the patients came from very far away -- I had patients come as far as 250 miles -- I did ask them to stay overnight initially because this was very early on in the trial and I really wanted to keep them around for 24 hours. Subsequent patients and some that I'm treating right now on another study I let go home at the end of the day now because I feel comfortable with that.

DR. PELUSI: The reason that I ask that is many of the patients that I particularly deal with come from very long distances.

The other question also becomes, when you look at the criteria for patients that would utilize this, is there a concern for you in those that refuse other modalities because maybe other modalities would ensure that they have to stay in another town for six weeks, seven

weeks in terms of other treatments? Do you see that actually bringing more patients to utilize this medication versus utilizing other forms of treatment that may be indicated?

DR. MILLS: I guess that's a difficult question for me to answer. You know, when I counsel a patient I give them their treatment options, and I really let the patient make their informed decision on that. You know, if the patients have systemic metastatic disease in this setting, I would really push them for systemic therapy if they're a candidate. In fact, all the patients I treated failed at least one or, in some cases, two or three types of chemotherapy. And I think that still is the number one management tool that we use in this patient population

But there are patients where the local disease itself -- it's just like a patient with a cord compression. Maybe they've got breast cancer but now they've got a cord compression. Well, we're going to take care of that local problem in a brief period of time and then put them back on their treatment. That's sort of how I view this product if I get to use it in the clinic. The patient has an obstructing lesion, I'll treat it with this product, and then go on to another therapy or another therapeutic option in the future.

DR. PELUSI: And just one last question. In

terms of symptom management, as you ran both of these trials, were there standard protocols for the different types of symptoms that were experienced, so we know if indeed this comes on the market how best, if there is a best way to treat some of these symptoms?

DR. MILLS: I don't recall right offhand. It was just recommended good medical management in these patients for their pain. All my patients took an oral opioid, oxycodone, something like that.

It brings up another point, though, that I wanted to make, and I think Dr. Kelsen was really concerned about this earlier. Even though these patients may have had pain locally here, they had other symptoms and other things going on elsewhere, which can sometimes confound things, as we know.

I had patients that did benefit from pain relief and a significant decrease in narcotic consumption, but couldn't score a hit on this fourth step because even though they said, yeah, I'm better, my pain's better, I'm not taking breakthrough medication, they're still taking medication, and maybe taking it because they have other problems elsewhere as well.

DR. PELUSI: Thank you.

DR. NERENSTONE: Dr. Przepiorka.

DR. PRZEPIORKA: Three questions, if I may. I

believe I heard that patients who had multiple tumors could be treated with multiple tumors at the same time, but you only followed the MTT for response. How many patients were treated for multiple tumors, and did you see any responses in the non-MTT that did not occur in the MTT, or vice versa?

DR. HOWELL: You are correct. The protocol permitted multiple tumors to be treated, and we do have data on that available.

Dr. Leavitt.

DR. LEAVITT: Yes, we do have those data. The response rate in all treated tumors is very similar to the response rate for the MTT. In fact, it did prove that the tumors that were chosen as the MTT were also the most difficult in which to obtain a response.

DR. PRZEPIORKA: While you're waiting for the slide, just the second half to that question. I also believe I heard that patients had systemic disease and would be treated with chemotherapy. Was that the same time they were on this protocol, or was systemic chemotherapy held until the end of this treatment?

DR. LEAVITT: In no case during this protocol did we give concurrent systemic chemotherapy and cisplatinum/epinephrine gel. If patients were candidates for systemic chemotherapy and they needed system

chemotherapy, they were not and should not have been entered on this protocol. We did have patients who completed this protocol and then subsequently developed more problematic distant disease, or first had noted systemic metastases, then went on for chemotherapy, but no, there was no delaying tactic here.

I do want to answer your question about all treated tumors. Now, these are patients who were stratified according to the most troublesome tumor size. And now looking at all of the tumors that were treated, not just the most troublesome tumor, the overall response rate is 30 percent for stratum 1 and 2. Stratum 1 I patients had 36 percent, 18 percent overall. And you can see the total number of tumors treated is 227.

DR. PRZEPIORKA: The draft package insert indicates that you would recommend a maximum of 10 mls of the gel per treatment. But your table indicates that patients received a median of 1 to 2 mls per treatment, with a maximum, in some of the studies, of 8 mls. How much data do you have in the 7-10 range to really support its safety?

DR. HOWELL: The vast majority of the patients were dosed with a median of 10 milligrams per meter squared of total platinum dose. The choice of 40 milligrams total dose as the recommended upper limit for any one treatment

session simply was based on systemic toxicity safety concerns, and we didn't want to get into a situation where we were exposing the systemic circulation to a large volume of tumor. The principle on which this whole approach was based was to try to decrease systemic exposure while at the same time increasing tumor exposure.

Does that address the issue, or would you like to see some data?

DR. PRZEPIORKA: Well, I guess you just indicated that most of your patients were treated with 25 percent of what you are recommending as the maximum dose, so I wanted to know how much data do you actually have to support the safety of going up higher than that to the maximum dose that you recommend.

DR. HOWELL: Let me ask. Do we have data on that point?

DR. ELIAS: Well, the toxicity and the AEs we reported are across the range on an intent-to-treat basis, before the amendment, after the amendment, larger tumors, and included larger tumors that would not be included in the current labeling indication, included tumors that were larger than 20 centimeters cubed, as well as included patients treated at the original 0.5 dosage level. The systemic toxicities in any case were very modest and not at all comparable to what's seen with systemic intravenous

cisplatinum.

Why don't we go ahead and look at slide 238. This shows adverse events by cumulative dose, which perhaps goes the most directly to your question. Now, in understanding the slide you need to remember that this includes a factor of time. In other words, it's cumulative dose over time. So, patients who had the larger doses cumulatively also may have included patients who are on study longer.

Nonetheless, the differences are there but are relatively modest. I believe you were mainly concerned about the nausea and vomiting, and in patients who had the larger dose range, this goes up to a maximum of about 33 percent. Again, this is all grades, and it needs to be compared to the placebo of 10 percent.

So, the dose-response effect is probably there but is relatively modest. I think the data well supports dosing within the range that we would intend to be included in the labeled indication.

DR. PRZEPIORKA: And my final question is, what are your plans for educating physicians on how to administer this?

DR. HOWELL: Dr. Leavitt?

DR. LEAVITT: We think that this is a unique form of therapy, and that with the availability of

IntraDose for the treatment of patients with advanced head and neck cancer, we think that there should be an education program. This should involve both medical meetings and presentations and should involve medical grand rounds, surgical grand rounds and similar kinds of programs. We are committed to making sure that physicians, be they medical oncologists, otolaryngologists, head and neck surgeons, have thorough understanding of the treatment methodology, the patient selections that are appropriate based on the studies that we've shown you, and the appropriate use of the product, and any of the side effects to expect and how they should be managed. Matrix will support this product in the marketplace.

I'm sorry that I couldn't give you a direct answer to an earlier question about previous chemotherapy, and I don't have the numbers of patients who had had previous cisplatinum for relapse. I do have some information on the patients who had had any chemotherapy at the time of relapse. Much of that was systemic cisplatinum. Would that be helpful to you?

DR. LIPPMAN: No. I was really interested specifically in the platinum.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: Thank you. I have two questions. First, perhaps for the study statistician.

Could you comment on the rationale for having two very small trials going on in parallel with a 2 to 1 randomization? What were your thoughts on that, since most of the analyses that have been presented are pooled analyses? And what were your early stopping criteria for those trials?

DR. STEWART: Well, to take the first question first. We don't consider that these were small trials. This is a rare disease. It's an orphan indication, and I'd like to point out that it took about six years to fully enroll each of these trials.

The reason for the sizing of the trials, the 90-patient total sample size in each trial with the 2 to 1 randomization was based, as was mentioned in the presentation, on ability to detect a difference in most troublesome tumor response rate of about 30 percent between the placebo, which of course we didn't expect to respond at all, and the CDDP/epi gel treated tumors.

DR. ALBAIN: Why did you not just do one trial? You had two trials going on. Since you presented pooled analyses.

DR. STEWART: I believe that this has been touched on earlier, but maybe not in enough detail. We wanted to do two randomized placebo-controlled trials to meet the regulations for product registration. Because of

the shift in the importance of patient benefit as an endpoint, we were well into the trials before it became apparent that we were going to be required to be statistically significant. The logical thing to do in a case like that is to pool the data, especially when you have identical trials.

DR. ALBAIN: Did you have early stopping rules? I may have missed it in your briefing book.

DR. STEWART: Yes. I'm glad you brought that up. We did not have a formal stopping rule for either of the trials, and there was a reason for this. We had a data safety monitoring board which regularly reviewed the data. Every six months they reviewed the data from both trials, and they reviewed the data in an unblinded fashion. We weren't allowed to be there when they were looking at the unblinded data. And all of the members of the data safety monitoring board had no affiliation with Matrix, other than being our consultants to be on the data safety monitoring board.

It was at their recommendation, actually at the recommendation of Dr. Steve George, when he agreed to serve as the statistician on our DSMB, that we not have a formal stopping rule because he felt that, in some ways, it tied the committee's hands. They wanted to be able to assess the data on an ongoing basis and be flexible with regard to

the recommendations they made.

DR. ALBAIN : Thank you.

My other question has to do with dose again. We heard that there probably is not so much a need to consider dose response in the way we usually think of it for higher doses, but what about lower dose? Is there a lower dose boundary for efficacy? Are we concerned at all because of these issues of leakage that we've heard about, this nonsignificant trend that a lower dose may not have as high a response rate in those tables we saw earlier, I think in Dr. Lippman's questions? Is there any data to reassure us that with learning curves, with some dose leakage, and at this lower dose after the amendment, that there still is reasonable efficacy?

DR. HOWELL: Let me start answering that question by just saying that remember that if some of the drug leaks on the first injection, you get the opportunity to come back a week later, after the tumor has reduced in some volume, because you killed some part of the tumor and you get a chance to give it a go again. And that's just the practicality of the clinical reality. Some of these tumors accept the full planned dose and some of them don't. Because of the heterogeneity of tumor size, consistency, location, that isn't invariable; it's easily controlled.

But the bottom line is that in the end you have

a pretty good response rate, even given the limitations of trying to be sure that the drug is getting into each tumor on each injection.

DR. ALBAIN: But do we know that we even need this lower dose? I guess I'm trying to get at, have we done some studies, perhaps some small phase II studies, that you need at least a certain dose?

DR. HOWELL: No. We do have phase I clinical trial data, and I'll ask Dr. Leavitt to address that. But from the basic pharmacology of cisplatinum, when you're introducing drug at this kind of concentration, any part of the tumor that is accessed by 4 milligrams per milliliter cisplatinum is going to be injured, even if it's not a large fraction of the tumor. That part of the tumor that's accessed is going to be injured.

A phase I dose-ranging trial was performed. Would you like to see the data on that?

DR. ALBAIN: Summarize it, perhaps.

DR. HOWELL: The summary is that dose-ranging was done over quite a wide range of things, and that trial included a variety of different tumor types, as well as patients with head and neck carcinoma, and the dose range of .25 milliliters per cubic centimeter of tumor volume simply turned out to be something that in head and neck tumors, with their slightly more scarce qualities, was on

the average reasonably well accepted.

DR. NERENSTONE: Dr. Couch.

DR. COUCH: My question is regarding patient selection, which is always a critical issue when you have these novel therapies. In the introduction it discussed that the patients that had obstruction, especially airway obstruction, would be potential candidates. According to your background package, the majority of tumors were in the neck, and these were the ones that I would think would be most likely to obstruct the airway.

My concern is that I'm worried that you're not going to be able to define the proximity of injecting this near the carotid arteries, which is certainly in the neck. For instance, after total laryngectomies, the carotid arteries are medialized and there's not much soft tissue there.

And then also the other issue is the wound. There is a worsening of the wound with eschar, a necrosis and erosion, so you don't want to have wound problems near the great vessels either.

Is there going to be a way that you can help physicians best select patients that will keep them out of trouble, especially in these cervical lesions, which unfortunately don't seem to respond as much as the facial and oral lesions?

DR. HOWELL: Let me ask Dr. Mills to give you a specific example of that situation and then Dr. Wenig to comment as a surgeon on how the anatomy --

DR. COUCH: I guess what I'm really getting down to is in your exclusion you say in close proximity to carotid artery. I really think it might be important to better define that.

DR. HOWELL: Let me address that issue exactly.

DR. LEAVITT: I'll comment from the medical oncologist's perspective, and also Dr. Wenig from the surgical perspective. He was also involved in these trials.

You are right. When these tumors do recur in the neck, involvement of the carotid artery can be a major problem. This is obviously a patient who would not be a candidate -- not be a candidate -- for therapy. And this is a large necrotic tumor, a stratum 3 tumor, if you would, with obviously carotid involvement at this point in time. I think when I screened patients with cervical disease, I obtained to CT scan, and that was my first step.

The carotid does tend to migrate medially in these patients who've had a lot of neck surgery. Here is a tracheostomy and here is a peristomal recurrence, and the carotid is right there, but there is a definite strike between the tumor and the carotid so there is clear

separation. I like to see a very good separation from the carotid in any tumor I would consider treating in the neck, and I think this is where the CT is very important. I use the CT to not only help me define the anatomy, but also on your physical exam, the length and width were very easy. Sometimes the depth or height was confusing, and the CT could help us right there on our initial planned treatment dose, to make sure that our physical exam was correct.

I'll ask Dr. Wenig if he'd like to expand on that from the surgical perspective.

DR. WENIG: I'm Barry Wenig from Northwestern University.

By way of background, I treated 4 patients on the 414 North American study, and I treated 1 subsequent patient on the follow-up study. So, I have a total of 5 patients with hands-on experiences.

This is an example of a patient treated from Europe. It's not my patient. But I think it's fairly representative because it points out several factors. Your question about the neck wound care is illustrated here. In this first slide, I think in my experience certainly, and I'm sure in yours, when tumors recur in the neck, there is often breakdown of the skin, and if not the skin, then certainly there is wound breakdown in some way, shape, or form. So, we're obligated to treat those patients or take